Clinical diversity and treatment approaches to blastic plasmacytoid dendritic cell neoplasm: a retrospective multicentre study

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Abstract: BACKGROUND Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a rare, aggressive type of hematologic precursor malignancy primarily often manifesting in the skin. We sought to provide a thorough clinical characterisation and report our experience on therapeutic approaches to BPDCN. METHODS In the present multicentric retrospective study, we collected all BPDCN cases occurring between 05/1999 and 03/2018 in 10 secondary care centres of the German-Swiss-Austrian cutaneous lymphoma working group. RESULTS A total of 37 BPDCN cases were identified and included. Almost 90% of the patients had systemic manifestations (bone marrow, lymph nodes, peripheral blood) in addition to skin involvement. The latter presented with various types of cutaneous lesions: nodular (in more than 2/3) and bruise-like (in 1/3) skin lesions, but also maculopapular exanthema (in circa 1/6). Therapeutically, 22 patients received diverse combinations of chemotherapeutic regimens and/or radiotherapy. Despite initial responses, all of them ultimately relapsed and died from progressive disease. Eleven patients underwent hematopoietic stem cell transplantation (HSCT; autologous HSCT n=3, allo-HSCT n=8). The mortality rate among HSCT patients was only 33.33% with a median survival time of 60.5 months. CONCLUSION Our study demonstrates the clinical diversity of cutaneous BPDCN manifestations and the positive development observed after the introduction of HSCT.

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Title

Clinical diversity and treatment approaches to blastic plasmacytoid dendritic cell neoplasm: a retrospective multicentre study

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Abstract

Background: Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a rare, aggressive type of hematologic precursor malignancy primarily often manifesting in the skin. We sought to provide a thorough clinical characterisation and report our experience on therapeutic approaches to BPDCN.

Methods: In the present multicentric retrospective study, we collected all BPDCN cases occurring between 05/1999 and 03/2018 in 10 secondary care centres of the German-Swiss-Austrian cutaneous lymphoma working group.

Results: A total of 37 BPDCN cases were identified and included. Almost 90% of the patients had systemic manifestations (bone marrow, lymph nodes, peripheral blood) in addition to skin involvement. The latter presented with various types of cutaneous lesions: nodular (in more than 2/3) and bruise-like (in 1/3) skin lesions, but also maculopapular exanthema (in circa 1/6). Therapeutically, 22 patients received diverse combinations of chemotherapeutic regimens and/or radiotherapy. Despite initial responses, all of them ultimately relapsed and died from progressive disease. Eleven patients underwent hematopoietic stem cell transplantation (HSCT; autologous HSCT n=3, allo-HSCT n=8). The mortality rate among HSCT patients was only 33.33% with a median survival time of 60.5 months.

Conclusion: Our study demonstrates the clinical diversity of cutaneous BPDCN manifestations and the positive development observed after the introduction of HSCT.

Introduction

Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a rare aggressive hematological malignancy (incidence 0.40-0.45/1,000,000), accounting for 0.44% of all hematological malignancies and 0.7% of cutaneous lymphoma cases [1]. Upon its first description in 1995, BPDCN was designated agranular CD4+ natural killer (NK) cell leukemia due to its characteristic surface marker profile (CD3-CD4+CD56+CD15+) and unique agranular morphology [2-4]. It subsequently became evident that BPDCN is a neoplasm of plasmacytoid dendritic cell (pDC) precursor cells now recognized as a distinct category/entity in the 2016 revision of the World Health Organization classification of tumours of hematopoietic and lymphoid tissues [5, 6].

Skin is the most commonly primarily affected target organ in BPDCN. Cutaneous lesions range from plaques and nodules to generalized patches and bruise-like lesions [7]. Besides involvement of peripheral blood and bone marrow (BM), found in about 45% of the cases, various organs (e.g. central nervous system, lungs, breast, gallbladder) can be affected [7-12].

Histologically, BPDCN lesions consist of infiltrates of medium-sized blastic cells with irregular nuclei. Besides the pDC markers TCL1, CD123 and/or CD303 (BDCA-2) [13], BPDCN express CD4 and CD56 (although aberrant phenotypes, i.e. CD4-CD56-, have been reported).

Therapeutic strategies for BPDCN are diverse as there are currently no consensus treatment guidelines. Fairly limited success (median survival of only 12-14 months [14, 15]) was achieved with chemotherapeutic regimens, but more recently, promising results have been reported with hematopoietic stem cell transplantation (HSCT) [16, 17]. Several studies indicate a curative potential and/or improved survival following both allogeneic and autologous HSCT [16, 18, 19]. It is still debatable which one of the two HSCT modalities may be superior for the treatment of BPDCN. The benefit of novel agents such as the BCL2-inhibitor Venetoclax or the NFkB-pathway inhibitor Bortezomib is currently being investigated [20-24].

In the present retrospective multicentric study, we analysed BPDCN cases collected by members of the cutaneous lymphoma working group of the Arbeitsgemeinschaft Dermatologische Forschung (ADF). We aimed to provide a comprehensive analysis of

the varying clinical presentations of BPDCN and to describe the current expertise on BPDCN treatment regimens, importantly including HSCT.

Study Design

We conducted a multicentric retrospective study within the German-Austrian-Swiss cutaneous lymphoma working group of the ADF. We identified BPDCN cases diagnosed between May 1999 and February 2018 in 10 secondary care centres (Supplementary Table 1) in Germany (5 centres), Switzerland (1 centre), and Austria (4 centres).

All identified patients with BPDCN (definition according to the International Classification of Diseases, 11th Revision (ICD-11) Code 2A60.5) were included in the study. The study was conducted according to the ethical guidelines at the respective institutions and the Helsinki Declaration. Data protection according to the EU and Swiss standards was guaranteed and enforced for all study patients.

Results

Demographics and patient characteristics

We retrospectively identified a total of 37 classical CD4+/CD123+/CD56+ BPDCN cases in 10 centres over a period of 19 years (Table 1, Supplementary Table 1). The mean age at diagnosis was 67.2 ± 14.9 years. 78.4% of the included BPDCN patients were male (male-to-female ratio almost 4:1). Male patients were about six years older (68.56 ± 13.90 years) at the time of diagnosis as compared to female patients (62.39 ± 17.07 years).

Diagnosis and manifestations

From a total of 37 patients, more than 90% (n=34) had skin manifestations at the time of diagnosis (Table 1). Almost 30% of the patients (n=10) experienced fever, night sweats, and/or weight loss (B symptoms). Three patients without skin manifestations presented with B symptoms only. About 90% of the patients (n=33) had additional organ involvement at the time of diagnosis, defined by confirmed invasion by blastic pDC precursors at the time of diagnosis. Such involvement included bone marrow (BM; 59.46%) or peripheral blood (PB; 29.73%). 27.03% of the patients presented with lymphadenopathy and 21.62% with splenomegaly. The mean time lapse between symptom onset and diagnosis, documented for 20 patients, was 9 weeks (range 4 - 24 weeks).

Characterisation of skin lesions

Regarding the nature of cutaneous manifestations, bruise-like lesions (haematoma, purpura and petechia), patches, erythematous to livid nodules, and maculopapular rashes were reported (Figure 1A-C). About 75% of the patients had nodules and/or plaques (n=28). Approximately 35% exhibited bruise-like skin lesions (n=13) or maculopapular exanthema (n=13), respectively. Almost half (45.95%) of the patients presented with more than one type of skin lesion (Supplementary Figure 1). Importantly, the time lapse between symptom onset and diagnosis was longer in patients with bruise-like as compared to nodular or plaque-like lesions (Table 2). This diagnostic delay was not associated with more severe disease.

Regardless of the nature of cutaneous manifestations, pruritus was rarely reported (only ca. 5% of all patients). Concerning the distribution of skin lesions (Figure 2), trunk involvement was most frequent (n=29). The extremities were affected in about 50% of the cases (n=19). The face commonly exhibited maculopapular rashes (53.80%) but was mostly spared in other types of skin lesions. One patient exhibited BPDCN lesions in the nasal mucosa.

Comorbidities: malignancies

Almost 40% of the patients (n=14) had additional concomitant malignancies, which were either haematological (n=7) or non-haematological (n=8; 7 patients). None of the patients concurrently had an additional hematological and non-hematological malignancy, but one patient had concurrently two non-hematological malignancies - a melanoma and a mammary carcinoma. Haematological malignancies included acute lymphoblastic leukemia (n=2), acute myeloid leukemia (n=1), Hodgkin's lymphoma (n=1), non-Hodgkin lymphoma (n=1), and myelodysplastic syndrome (n=2). There was no association between BPDCN and a particular type of non-haematological malignancy (Table 3).

Treatment regimens of two decades

In terms of first-line treatments, about 70% (n=22) of the patients received a broad range of chemotherapy regimens (Table 1, Supplementary Table 2). Radiotherapy alone or in combination with systemic agents was applied in 3 patients. Eleven patients underwent HSCT (more details below). For three patients no disease specific treatment was recorded, either due to lost to follow-up (one patient) or due to fulminant disease progression, which necessitated immediate palliative care (two patients).

Our 16 patients treated after 2008, i.e. half-time of our retrospective analysis (Figure 2A), had a significantly better overall survival as compared to those treated in and prior 2008: 20.3 months (range: 1.6-76.2 months), with six patients still alive, versus 10.7 months (range: 3.87 – 25.3 months). These differences could not be attributed to age, gender or skin lesion type / organ involvement. In contrast, there were major differences in terms of treatment approaches between the prior/after 2008 cohorts: 11 out of 16 patients treated after 2008 received HSCT (vs. none of those prior 2008), which was associated with significantly better progression-free survival (see further).

Survival following chemotherapies

The majority of patients responded to first-line chemotherapies (listed in Supplementary Table 2): three patients achieved complete remission, 11 partial remission and two had stable disease (Table 1). Progressive disease was observed in six patients. All patients eventually relapsed, with a mean progression-free survival of less than a year (6.5 months; range: 0.5 – 19.7 months). Regarding the type of chemotherapy (Supplementary Table 2), five patients received an AML-, two an ALL- and twelve a ~~lymphatic~~ lymphoma regimen. Patients receiving the latter had a better overall and progression-free survival (Figure 2B).

Second-line treatments included alternate chemotherapeutic regimens, single-agent or combination therapies, and radiation (Supplementary Table 2). Twelve patients with a relapse did not receive a second-line treatment. All patients solely undergoing chemotherapies and/or radiotherapy eventually died from progressive disease. Mean overall survival was 8.67 months (range: 0.5 - 23.9 months).

Therapeutic success of allogeneic and autologous HSCT

A total of 11 patients underwent HSCT, all of them were treated after 2008: eight received allogeneic and three autologous HSCT (allo-HSCT: n=8; auto-HSCT: n=3; Table 3). Patients receiving auto-HSCT were older (75.3 ± 12.13 years) as compared to allo-HSCT patients (46.6 ± 15.54 years). The male-to-female ratio was 2:1 for auto-HSCT and 3:1 for allo-HSCT, respectively. The mortality-rate among HSCT patients was 33.33% with no difference between allo- and auto-HSCT recipients (2 allo-HSCT recipients were lost to follow-up and thus excluded from the analysis).

As for the auto-HSCT patients, one patient relapsed within five months post-HSCT and died from progressive disease despite a salvage therapy with hydroxyurea. At the study closing date (1st of July 2019), the other two patients were still in complete remission and alive, with a follow-up of 174 and 884 days, respectively. Of the allo-HSCT recipients, two died within eight months post-HSCT (one from therapy-refractory graft-versus-host disease, for the second patient the cause of death was not reported). Two allo-HSCT patients were lost to follow-up. The other four allo-HSCT recipients remained relapse-free

(various lapses of follow-up, i.e. between 156 and 2253 days post-HSCT) at least until the study closing date (1st of July 2019).

Discussion

BPDCN is a very rare and aggressive haematological malignancy manifesting primarily mainly in the skin and presenting a major therapeutic challenge. This retrospective study encompassing a time period of approximately two decades reports on our experience with BPDCN patients from 10 centres belonging to the German-Austrian-Swiss network of cutaneous lymphoma. Herewith, we provide a thorough description of the clinical presentation of BPDCN and describe our experience with BPDCN treatment regimens, with an emphasis on HSCT.

Our cohort of 37 BPDCN patients had a male:female ratio of 4:1, i.e. double the percentage of males as compared to previous reports. BPDCN skin manifestations are the most common primary manifestation of the disease (in more than 90% of our patients) and highly diverse. Clinical recognition and biopsy of cutaneous lesions can enable an early diagnosis, which is clinically relevant, given the highly aggressive course of the disease. As reflected in our patient cohort, BPDCN lesions can be nodular, bruise-like or maculopapular in nature. The majority of our patients had nodules or plaques, similar to what has been reported [25, 26]). In contrast, we had more patients with bruise-like lesions (ca. one third) than in previous studies [25]. In addition, our study points out that almost half of the patients have more than one type of skin lesions. The longer time lapse between symptom onset and diagnosis among patients with bruise-like skin lesions underlines the difficulty to recognize this type of manifestation and the importance to consider BPDCN as a differential diagnosis of unclear cutaneous lesions and when suspecting cutaneous lymphoma and/or leukaemia cutis.

Involvement of at least one additional organ, i.e. BM, blood or lymph nodes, was observed in ca. 90% of our patients. None of them had central nervous system involvement, the prevalence of which had previously been reported to be 9-26% [25, 27-29]. Among our patients, those exclusively presenting skin lesions (n=4) did not have a better outcome. Although this limited number of patients does not allow for any conclusion, our observations differ from previous reports in that there is a slightly (but not significantly) better overall survival in this patient group [30].

The long coverage period (ca. 20 years) of our study reflects the diversity of therapies and concurrent differences in patient survival. This can mainly be attributed to the high proportion of patients receiving HSCT as a first-line option (11 out of 16). Previous observations show that despite considerable initial response rates, a long-lasting response cannot be achieved with chemotherapies. In a previous study [31], the survival of bone marrow transplanted BPDCN patients was significantly higher as compared to all other therapeutic choices (chemotherapy, radiation). In line with this, Weil et al found high-dose therapy followed by allo-HSCT could induce long-term remission, but due to the small number of auto-HSCT patients (n=5) did not draw conclusions in this regard [16]. Khardfan-Dabaja et al [17] found a lack of efficacy with autologous HSCT (in 8 patients). In our study, we did not observe outcome-related differences between auto- and allo-HSCT. With the low number of cases (3 auto- and 8 allo-HSCT patients) we however cannot draw definite conclusions as to this important issue. This needs to be addressed in a large prospective trial.

Taken together, our experience with 37 BPDCN patients demonstrates the spectrum of cutaneous manifestations with which BPDCN may present and that especially clearly confirms the superiority of HSCT over any type of chemotherapeutic regimen. The search for a matching donor for HSCT along with a swift aggressive course of treatment should be initiated as soon as diagnosis of BPDCN is confirmed.

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MCB, JV, RS, EG and NL performed the research. MCB, JV and EG designed the research study. MCB analysed the data. All the authors contributed essential tools (patient data collection) and wrote the paper.

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Tables

Table 1. Patient characteristics.

Clinical Presentation		
Demographics		
Age at first diagnosis, years		
Mean±SD		67.2±14.9
Sex, n (%)		
Female		9 (21.6)
Male		28 (78.4)
Clinical presentation at diagnosis		
Cutaneous involvement, n (%)		34 (91.9)
Nodules and plaques		28 (75.7)
Bruise-like lesions		13 (35.1)
Maculopapular rash		13 (35.1)
Nasal mucosa		1 (2.70)
Pruritus		2 (5.40)
Extracutaneous involvement		33 (89.2)
Peripheral blood		11 (29.7)
Bone marrow		22 (59.5)
Lymphadenopathy		10 (27.0)
Splenomegaly		8 (21.6)
B symptoms		10 (27.0)
Comorbidityies: malignancies		12 (32.4)
Non-hematological	7 (50.0)	
Hematological	7 (50.0)	
	ALL	2 (28.6)
	AML	1 (14.3)

	HL	1 (14.3)
	NHL	2 (28.6)
	MDS	2 (28.6)
Treatments		
Types of treatment		
HSCT as first-line treatment		11 (33.3)
Radiation as first-line treatment		2 (6.06)
Chemotherapy as first-line treatment		19 (57.6)
	AML regimen ALL regimen Lymphoma regimen	5 2 12
Other		1 (3.03)
Average time lapsed between diagnosis and start of first-line treatment		37.4 days
Treatment response		
Response to first-line chemotherapy, n (%)	CR	3 (15.8)
	PR	9 (47.4)
	PD	5 (26.3)
	SD	2 (10.5)
Relapse after first-line chemotherapy, n (%)	19 (100)	
Average overall survival of those receiving first-line chemotherapy (excluding LOFs), months	8.96	

Table 2. Involvement of body sites among and time lapse to diagnosis.

Type of skin lesion	Time to diagnosis (months mean ± SD)	% among patients	Body site involvement (%) HSCT type		
			Face	Trunk	Extremities
Nodules	5.1	30.0 (n=11)	20.0	86.7	66.7
Plaques	3.8	19.0 (n=7)	30.8	84.6	53.8
Bruise-like lesions	17.3	30.0 (n=11)	15.4	100	76.9
Maculopapular exanthema	8.5	25.0 (n=9)	53.8	84.7	61.5

Table 3. Comorbidities: Malignancies.

Type of malignancy	Cases (n)
Hematological	**7**
ALL	2
AML	1
HL	1
NHL	1
MDS	2
Non-hematological	**8**
Pulmonary carcinoma	1
Mammary carcinoma*	2
Prostate carcinoma	1
Primary cutaneous melanoma*	1
Bladder carcinoma	1
Thyroid cancer	1
Hepatocellular carcinoma	1

Abbreviations: ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; HL, Hodgkin's lymphoma; NHL, non-Hodgkin lymphoma; MDS, myelodysplastic syndrome.

* occurred in the same patient

Table 4. HSCT recipients.

Sex	Age	Induction	Conditioning	HSCT type	OS (days)
Autologous HSCT					
M	89.3	NA	NA	auto-HSCT	219
M	68.6	*age-adapted hyper CVAD	*HD BEAM	auto-HSCT	174+
F	68.0	*hyper CVAD	*HD BEAM	auto-HSCT	887+
Allogeneic HSCT					
M	40.9	*DAV 3+5+7	NA	allo-HSCT	260
M	65.0	*MICE	*S-HAM	allo-HSCT	288
M	56.4	*GRAALL-2014/B	RIC	allo-HSCT	156+
M	45.0	*CHOEP	NA	allo-HSCT+DLI	1815+
M	25.7	*DAV 3+5+7	*FLAG	allo-HSCT	2099+
F	30.3	*HOVON 102	MAC	allo-HSCT	2283+
F	42.1	NA	NA	allo-HSCT	LOF
M	68.9	gemcitabine	NA	allo-HSCT	LOF

*Chemotherapy regimens are detailed in Supplementary 1. Abbreviations: OS, overall survival; M, male; F, female; NA, not available; RIC, reduced-intensity conditioning; DLI, donor lymphocyte infusion; MAC, myeloablative conditioning; LOF, lost to follow-up.

Figure Legends

Figure 1.

Diversity of cutaneous BPDCN manifestations. (A) Multiple erythematous nodules on the chest and upper back. (B) Tumoral lesions on the face. (C) Bruise-like infiltrated patches on the back and right leg. (Photographs: Department of Dermatology, University Hospital of Zurich and Department of Dermatology, University Hospital Vienna).

Figure 2.

Comparison of logrank curves showing the survival (as percentage among all patients) of (A) of patients treated prior (n=11) vs. after (n=16) 2008 and (B) of patients who underwent AML- (n=5), ALL- (n=2) or lymphoma-regimens (n=12) of chemotherapy.

Figure 1.

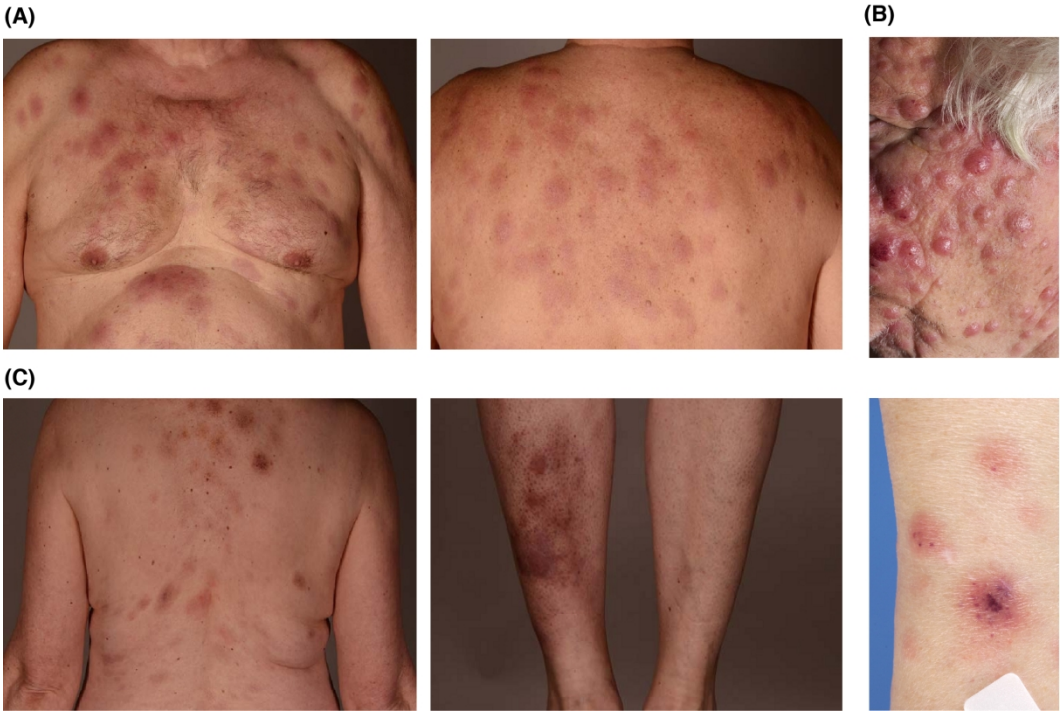

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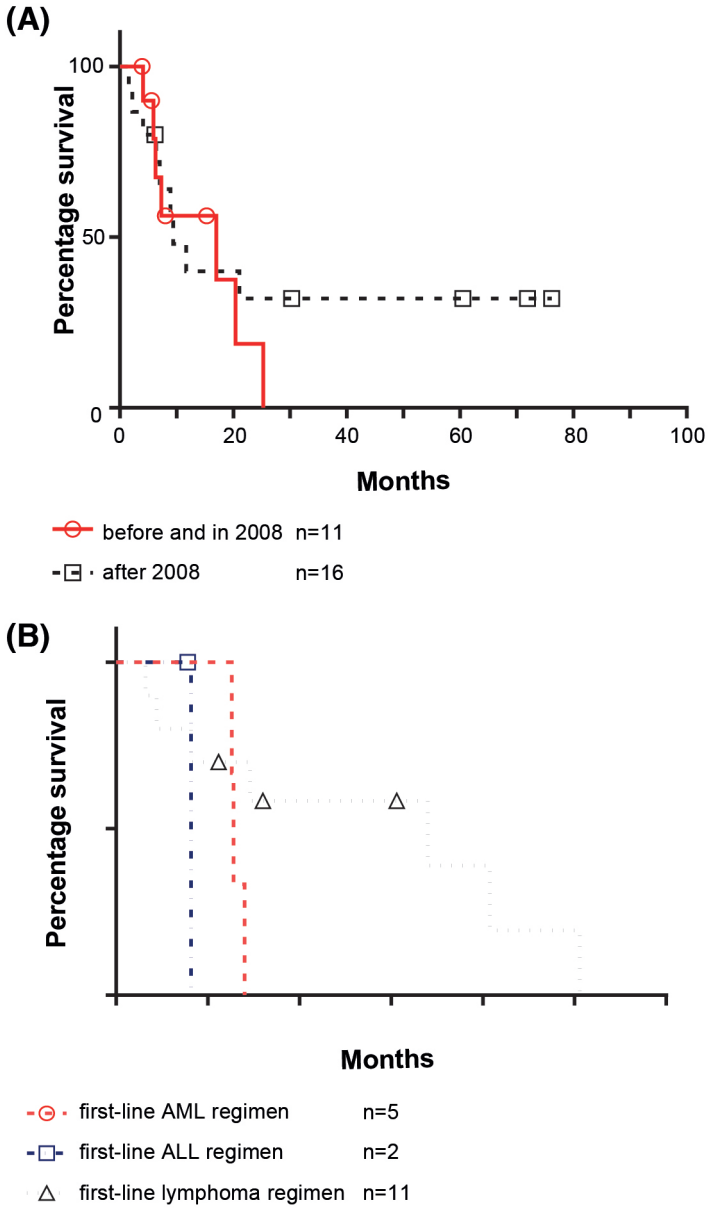
Figure 2.



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